



Markedly Elevated Bone Density in a Man with Longstanding Hypoparathyroidism

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Introduction

Recent studies (1, 2) have demonstrated that the effect of PTH on bone mineral density (BMD) is rather complicated. With the introduction of teriparatide for the treatment of osteoporosis, the relationship between PTH and BMD has been readdressed. Patients with primary hyperparathyroidism are well recognized to have demineralization of bone, particularly cortical bone such as is present in the distal third of the radius (3–5). Postmenopausal women who are given daily injections of whole molecule 1–84 PTH (1, 2) or teriparatide (1–34 PTH) (6) have an anabolic effect on bone, particularly of the trabecular type in the lumbar spine. This effect is also seen in males with a similar pattern of bone growth, predominantly in the lumbar spine (7, 8). Several reports of men and women with chronic hypoparathyroidism demonstrate modest increases in bone density (9–12). In this context, we present an 85-yr-old man with longstanding idiopathic hypoparathyroidism who had markedly increased BMD by dual energy X-ray absorptiometry (DXA) (T-score lumbar spine 10.6, total hip 4.2, total body 4.5). Peripheral quantitative computed tomography (pQCT) demonstrated a marked increase in the strength index value of the distal radius, most prominently of the distal 4%, which is primarily trabecular bone. He had no history of fracture. Laboratory studies revealed a decrease in bone turnover markers.

Case Report

This 85-yr-old white male has been followed at our University Hospital Metabolic Bone Clinic for idiopathic hypoparathyroidism since soon after it was diagnosed in 1976 by an incidental finding of a low serum calcium on routine laboratory work. Over the years, his control was excellent, while taking 500 mg calcium as carbonate three times a day along with 0.25 µg calcitriol twice a day and restriction of phosphate intake. In 2004 we obtained a bone density study because of his age and history of being on chronic phenobarbital therapy (remote history of a seizure), despite the fact he had lost little height since his youth and had sustained no fractures. He had no other medical problems except for hypertension, and had no family history of osteoporosis. He had been a professional engineer and a corporate executive, led an active, healthy lifestyle, and continues to play golf and tennis but never attempted to swim. He denied exposure to lead, fluoride, or any chemical or environmental toxin.

Physical exam was unremarkable except for mild scoliosis. He had a normal size and shape of his mandible, no kyphosis, and no torus palatinus. Chvostek and Trousseau signs were always absent.

After we obtained the results of his DXA, a work up for metabolic bone disease was initiated including serum chemistries, bone turnover markers, and LRP-5 gene analysis.

Methods

pQCT Methodology (13)

pQCT (Norland-Stratec XCT-2000, Stratec Medizintechnik GmbH, White Plains, NY) was used to determine cross-sectional geometry and volumetric density (vBMD) at three locations in the distal third of the nondominant forearm. Axial slice scans were made at 4%, 15%, and 30% of the forearm length as measured from the distal border of the radio-ulnar joint. A slice thickness of 2.3 mm, planar voxel size of 400 µm, and standard cortical and trabecular bone and soft tissue thresholds were used. For each slice the total, cortical, and trabecular vBMD, cross-sectional areas and strength index (density-weighted polar moment of inertia) were determined by the software. Comparison was made to reference data from a group of 39 male subjects with a median age of 30 (range 18–38) made in the same instrument and protocol.

Serum N-telopeptide and osteocalcin were assayed by Quest Diagnostics Nichols Institute. Bone-specific alkaline phosphatase was assayed by Esoterix. Other laboratory tests were performed by the Clinical Pathology Department, University Hospital, Syracuse, NY.

Exons 2–4 of the LRP5 gene, where defects have been shown to cause high bone density disease, were examined for mutations (studies were performed at the Division of Bone and Mineral Diseases, Washington University School of

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LETTER FROM THE PRESIDENT

Each time I leave one of the EFF scientific meetings where I have a chance to meet and spend time with groups of endocrine fellows, I feel energized by the experience. This past weekend (January 31st) was no exception when the EFF and The ADA presented a Scientific Forum before the ADA's PostGraduate Course in San Francisco. The faculty was superb, and the formal lectures coupled with workshops were outstanding with excellent interaction between the speakers and the attendees. Once again each faculty member told me how much they enjoyed talking with fellows from different programs around the country and asked to be invited again. It

points out to me how much senior physicians recognize the importance of what the Endocrine Fellows Foundations' programs are doing and how much your questions and interest excites them. It also confirms that the time, thought, and energy given by the EFF Board and staff is justified.

I clearly remember when there was no Endocrine Fellows Foundation and no attention was given to all of you, the future thought leaders, care givers, researchers, and educators. As a result of the EFF activities, other organizations have begun creating new opportunities for endocrine fellows. I am pleased that you all will be able to have more programs that will help you as you move forward with you careers. The Endocrine Fellows Foundation will continue to satisfy the unmet needs of fellows and we look to you to let us know new areas in which the Endocrine Fellows Foundation can be helpful to you and future fellows.

For the past 9 1/2 years, every fellow who has participated in the EFF activities has come to know Marilyn Fishman, the Endocrine Fellows Foundations Executive Director. She has been called the "mother of endocrine fellows" because she has been a central figure in the lives of every endocrine fellow with whom she has come in contact. From arranging every aspect of the scientific meetings to helping with applications for research and preceptorship grants, facilitating the publication of this newsletter, the web site, coordinating grant reviewers, and making travel and hotel arrangements for fellows, guest faculty, and the Board, and much more, Marilyn has been the fulcrum of the organization.

At the October Board meeting she announced that she will be retiring by July 1st of this year. There will be a significant void in the EFF when she leaves. Her imprint will be with us as long as there is an Endocrine Fellows Foundation. Marilyn's dedication, loyalty, integrity, and sincerity of purpose is recognized by whom ever she comes in contact. Members of the pharmaceutical industry, who have been so generous in helping the Endocrine Fellows Foundation fulfill its mission, have been engaged because of Marilyn's personality, passion, positive energy, and yes, persistence.

We will miss her, you certainly will miss her, and we wish her well in her new life in retirement, which I know will be filled with challenges that will be made better by her presence.

Sherman M. Holvey, M.D.
President, Endocrine Fellows Foundation



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EndoTrends

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Medicine, St. Louis, MO). Coding exons 2–4 and the adjacent mRNA splice sites of *LRP5* were amplified by PCR, using our patient's genomic DNA (from blood leukocytes), and sequenced in both directions. Primers used for PCR and DNA sequencing were reported in Gong *et al.* (14). DNA sequence chromatograms were examined visually and by using AlignX software (VectorNTI; Invitrogen, Carlsbad, CA).

Results

Initial BMD measurement revealed remarkably dense bone (Table 1). A repeat DXA using a Hologic QDR 4500 machine revealed confirmatory results.

Routine radiographs of the spine revealed a normal appearance with no compression fractures and minimal degenerative changes (Fig. 1A). Computed

tomography (CT) scan of spine and pelvis revealed mild to moderate increase in density with prominence of the trabeculae (Fig. 1B). A quantitative CT of the ultra-distal radius showed structurally strong bone with a strength index

value (density adjusted cross-sectional polar moment of inertia), which was 1.5 SD greater than the aforementioned younger control group. The strength

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	L1–L4	Total Hip	Total Body	Distal 3rd Radius
BMD (g/cm ²)	2.51	1.64	1.58	0.85
T score	10.6	4.2	4.5	–0.2
Z score	11.5	5.5	5.5	1.2

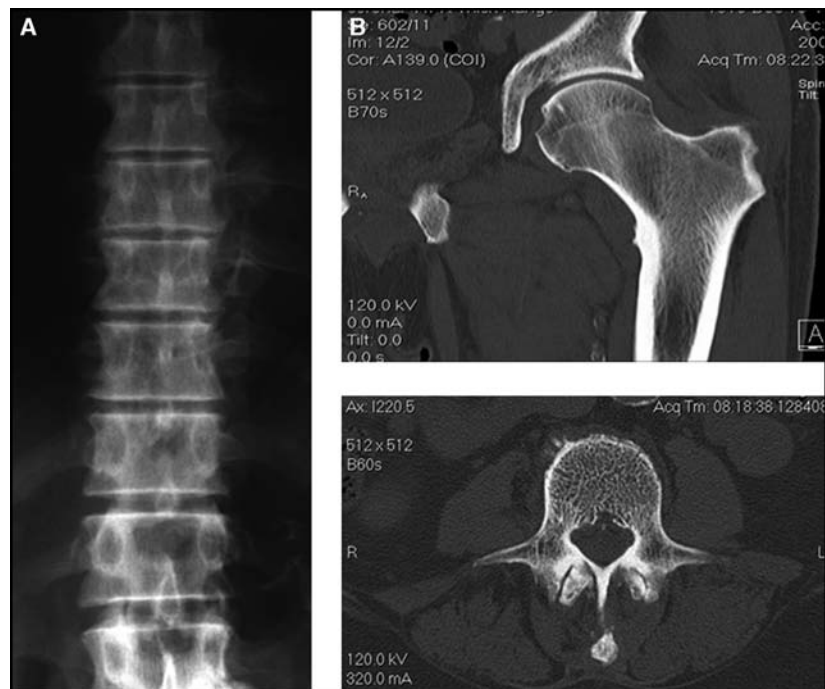


Figure 1. A, X-ray of the spine, showing straight, symmetric and well-delineated vertebral bodies, notable is the lack of degenerative joint disease or compression. B, CT of the spine and hip. Note prominence of trabeculae.

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index value of the distal 15% of the radius was 0.7 SD above the control values, whereas the distal 30% was -0.1 SD below control (Table 2).

Blood tests demonstrated low bone turnover markers (Table 3). Serum PTH was always undetectable. Other laboratory tests including serum lead, copper, fluoride, prostate-specific antigen, and CK-BB were either low or normal.

Gain-of-function mutations in exons 2–4 of the LDL receptor-related protein 5 (LRP5) gene have been identified as the cause of benign high bone mass and high bone mass disease, in familial and sporadic cases (15, 16–19). Accordingly, using genomic DNA from our patient, exons 2–4, and the adjacent mRNA splice sites were examined for mutations. However, no mutations were detected in exons 2–4 of the LRP5 gene that would explain our patient's high bone mass.

Discussion

Our 85-yr-old man with longstanding idiopathic hypoparathyroidism had markedly increased BMD by DXA with the greatest increase being in the lumbar spine (trabecular bone), the least increase being in the distal radius (cortical bone) and the intermediate increase being in the total hip (mixture of cortical and trabecular bone) (Table 1). These DXA values correlate with the strength index values obtained in the distal radius by pQCT where the strongest bone was in the primarily medullary area (distal 4%), was least in the primarily cortical area (distal 30%), and intermediate in the area of combined cortical and trabecular bone (distal 15%) (Table 2). Probably as a result of these structural properties of his bones, our patient had never sustained a fracture and had normal appearing radiographs.

LRP5 is a major component of the Wnt signaling pathway, which activates osteoblasts and promotes bone growth. Defects in *LRP5* affect bone accrual in two ways: 1) homozygous deactivating mutations found throughout the gene and inherited as autosomal recessive cause osteoporosis-pseudoglioma syndrome, a low bone density disorder

Table 2
Results of pQCT of the Radius

Site	Control Group		Subject Data	
	Mean	SD	Data Point	SD above Mean
Radius 4%	490.9	97	633.3	1.5
Radius 15%	412.6	86	476.9	0.7
Radius 30%	339.1	71.7	335	-0.1

(14), and 2) heterozygous activating mutations in exons 2–4 cause benign high bone mass in some families (15, 16) and high bone mass disease in others (17–19). Features of high bone mass disease, caused by gain-of-function *LRP5* mutation, can include prominent jaw, torus palatinus, neurological problems, dense skull, and thickened cortices of long bones (15–19). However, no mutations in exons 2–4 of *LRP5* were found in our patient; other genetic factors may be involved.

Patients with chronic hypoparathyroidism of several causes have had increased BMD primarily of the lumbar spine. Abugassa (9) reported on women who had hypoparathyroidism from surgery for thyroid cancer and for hyperparathyroidism and whose BMD was measured by dual photon absorption. The highest mean T-score of both groups of patients was at the lumbar spine where the T-score of the thyroidectomized patients was 1.21 ± 0.05 , and was 1.09 ± 0.03 in the parathyroidectomized patients. The highest T-score at all sites was not reported. However, the pattern was similar to our data with the greatest increase being in the lumbar spine, followed by the hip and lastly, the radius.

The Duan paper (12) reported on postmenopausal women with postsurgical (thyroidectomy) hypoparathyroidism. BMD measurements were compared with age-matched controls and showed higher mean values at the lumbar spine and proximal femur, but not at the distal radius. The T-score at the spine was 1.26 ± 0.1 (control group T-score = 1.07 ± 0.27), whereas the proximal femur showed a mean value of 0.97 ± 0.06 (control = 0.85 ± 0.01). Their study also looked at cortical bone and showed that these women had their bone loss slowed by the lack of PTH, when compared with age-matched controls.

Table 3
Serum Bone Turnover Markers Based on Mean of Multiple Assays

	Patient	Normal Range
Osteocalcin	12.4 ng/ml	(11.3–35.4)
BSAP	12 ng/ml	(2–24)
N-telopeptide	8.5 nmol BCE/liter	(10.7–22.9)

The Chan paper (10) reported on patients with idiopathic and postthyroidectomy hypoparathyroidism. The highest T-scores were at the lumbar spine with a mean of 2.06 ± 1.07 . The mean lumbar spine Z-score in patients with idiopathic hypoparathyroidism was 1.68 ± 0.32 . This paper also shows the greatest bone growth in the lumbar spine, and a lesser increase in the femoral neck. The radius was not measured in this study.

Our patient with longstanding idiopathic hypoparathyroidism had lumbar spine T and Z scores far greater than reported in the previous papers. He also had a markedly increased total body BMD. The increased BMD in our patient and those reported in the literature is primarily in trabecular bone and least in cortical areas. Our patient's BMD increases are much greater in magnitude, while maintaining a similar distribution.

The BMD changes between hypoparathyroid patients and those given intermittent PTH are similar, as described above. However, markers of bone turnover are opposite. Orwall *et al.* (7) looked at males given 1,34 PTH intermittently, and found a dose-dependent increase in bone turnover. This validates a similar observation noted in an earlier paper by Kurland *et al.* (20) A similar result occurred with 1,84 PTH, where bone turnover was increased in a dose-dependent manner (1, 2).

These results are in contrast to the low bone turnover markers we observed in our patient, and to results of patients with a hypoparathyroid state where markers of bone turnover are generally suppressed (21). It is important to emphasize that when comparing the endpoint of BMD, both hypoparathyroid patients and those treated with inter-

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mittent PTH display increased trabecular bone growth, most notably at the lumbar spine. However, bone turnover markers are suppressed in the former, whereas significantly elevated with either 1,34 or 1,84 intermittent PTH dosing. These data suggest different mechanisms for growth, with the similarity being a net difference between formation and resorption that leads to overall bone accrual.

Last and purely speculative, it is at least theoretically possible that suppression of parathyroid function induced by a calcimimetic may some day be found useful for the treatment of osteoporosis.

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Case Report

Profound Elevation in Thyroid-Stimulating Hormone and Increased Thyroid Hormone Requirements Associated with the Development of Nephrotic Syndrome

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Objective

To recognize nephrotic syndrome (NS) as a potential cause of increasing thyroid hormone requirements in patient with hypothyroidism.

Case Presentation

A 23-yr-old white female was diagnosed with primary hyperthyroidism (most likely Graves' disease) 6 yr ago. This was based on a low TSH level of less

than 0.03 μ /ml, elevated thyroid hormones levels, and diffusely increased radioactive iodine thyroid uptake of 65% at 24 h. There was no family his-

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tory of thyroid disease. This patient was treated with radioactive iodine ablation using 10 mCi of I^{131} . Within a few months, she responded to treatment and was started on supplemental levothyroxine (LT_4).

The patient's clinical condition was stable for 5 yr on a LT_4 dose in the range of 100–175 μ g daily with TSH levels within normal limits. However, in 2004, her LT_4 treatment was interrupted for several months due to financial issues and her TSH rose to 347 mU/ml. At this time, therapy was resumed and TSH levels came back to normal. In early 2006, she developed symptoms of profound hypothyroidism and elevated levels of TSH (102 mU/ml) while taking the same maintenance dose of LT_4 (150 μ g daily). She was taking her thyroid medication daily, while fasting, and without any other medications, vitamins or calcium supplements. She also denied taking proton pump inhibitors, or antacids. Despite the increased dose of LT_4 (up to 300 μ g daily), her TSH level rose to 308 mU/ml and her free T_4 (FT_4) decreased to 0.58 (RR 0.71–1.85) ng/dl, and her free T_3 (FT_3) level dropped to 0.5 pg/ml (RR 2–4.2). Her reverse T_3 (rT_3) levels were also low at 19 pg/ml (RR 90–350). Thyroid peroxidase antibodies were negative.

During the same period of time, she was diagnosed with NS due to membranous glomerulonephritis associated with retroperitoneal fibroses of unknown etiology. Her 24-h urine protein reached 12 g and her serum albumin level went down to 0.8 g/dl, whereas her creatinine level stayed in the normal range. She had a significant loss of thyroid hormones in the urine, as estimated by total T_4 , which was 3.9 μ g/dl and total T_3 , which was 29 ng/dl.

The NS was treated with mycophenolate mofetil (cellcept) and high-dose prednisone. In addition to these, an angiotensin converting enzyme inhibitor for the proteinuria, a statin for newly diagnosed hyperlipidemia, and a loop

diuretic for pitting edema were also initiated. The proteinuria responded partially to treatment. Following the same trend, LT_4 requirements decreased and both the thyroid hormones levels and the TSH level returned to normal.

Discussion

We present an interesting case of a young woman with postradioactive iodine ablation hypothyroidism who became very resistant to treatment (with recurrence of clinical and biochemical hypothyroidism) in conjunction with the development of NS. Her TSH remained elevated in spite of a large replacement dose of LT_4 and at the same time the amount of thyroid hormone in her urine was elevated.

Most of the T_4 and T_3 in the blood are bound T_4 -binding globulin (TBG). Smaller amounts are bound to albumin and transthyretin, which is also called T_4 binding prealbumin. In normal conditions, there are negligible amounts of T_4 and T_3 in the urine because of the limited filterability of the hormone-binding protein complexes. In NS, TBG and transthyretin are excreted in addition to albumin (1, 2). An albumin level in a patient with NS can be used as a surrogate for the TBG level. T_4 and T_3 are excreted in significant amounts in the urine along with the lost protein. Moreover, there is a significant correlation between the serum level of albumin and serum levels of both total T_4 and total T_3 (3). Most patients with a normal thyroid who develop NS have normal or slightly high TSH. Serum T_4 and FT_4 are usually normal, while serum T_3 and FT_3 are usually decreased (1). However, in severe cases of NS, primary hypothyroidism can occur even in the absence of thyroid disease. Also, patients with primary thyroid failure who take LT_4 and develop NS rarely present with increased LT_4 requirements (4). Interestingly, in our patient, the increased requirement of thyroid hormone as indicated by increased TSH levels preceded the clinical diagnosis of NS. The magnitude of TSH elevation when the

patient had NS and was taking her medication was comparable to TSH elevation when she did not have NS and did not take the medication for a few months due to financial issues. Doubling the dose of LT_4 did not help in restoring euthyroxinemia. This finding is consistent with previous reports which showed that exogenous thyroid hormones usually fail to correct the situation unless the kidney problem is solved (5). The pathophysiology of hypothyroidism in the context of NS is generally believed to be due to rapid urinary elimination of the protein-bound thyroid hormones. Nevertheless, other factors such as iodine deficiency and changes in the biosynthesis, binding to carrier proteins, and metabolism of T_4 and T_3 might play a role (1).

Conclusions

Most patients with NS have normal thyroid function tests. However, cases of profound hypothyroidism may occur in patients of severe NS or in patients of limited thyroid reserve.

Exogenous thyroid hormone usually does not correct the hypothyroidism due to continuous urinary loss. Furthermore, improvement in proteinuria results in lower requirements of thyroid hormones.

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Elevated High-Density Lipoprotein

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Introduction

A 54-yr-old woman was referred to the lipid clinic for evaluation of an abnormal lipid profile. Her primary care physician had noted a very high high-density lipoprotein (HDL) level on routine preventive screening. The primary care physician was concerned that a very high HDL cholesterol level could be indicative of a lipid disorder and that excess cardiovascular risk may be associated with the lipid abnormality.

Description

The patient was a 54-yr-old Caucasian woman being evaluated for a high serum HDL level. The woman related that her HDL levels had been high on previous testing over the years. She has never been placed on lipid medications. She related no serious health problems. She undertakes regular physical activity with daily exercise on a treadmill walking at a brisk pace. She has never experienced chest pains, unusual shortness of breath, weakness or numbness of the extremities, nor any slurring of speech or difficulty swallowing. She has never undergone formal cardiac stress testing.

She has an identical twin sister who also has elevated HDL cholesterol. Her sister had undergone a medical evaluation and was told that she had “large” lipoproteins and was placed on statin therapy. Her sister has never been diagnosed with cardiovascular disease and has a similar exercise tolerance as the patient. Her father has a history of coronary artery disease and suffered a myocardial infarction at age 72. Her mother lived to the age of 84. She reports that many members of her mother’s family are long-lived. There is no history of cardiovascular disease in her mother’s family.

She reported no other medical problems and takes only a daily multivitamin and calcium with vitamin D. She

has no drug allergies. She has never smoked and on average has an alcoholic beverage once a month. She eats a serving of meat, veal, or pork five times a week and has five to seven servings of eggs each week. The patient is married with no children. She works as a project manager at a local bank.

On physical examination the patient was a thin, physically fit appearing Caucasian woman. Her blood pressure was 110/70 with a pulse of 65. Her height was 5 ft 2 in. with a weight of 105 lbs and a body mass index of 19.5. Her cardiovascular exam revealed a regular rate and rhythm with no murmurs rubs or gallops; the radial, femoral, dorsalis pedis and posterior tibialis pulses were symmetric and there were no carotid or femoral bruits. The remainder of her physical exam was normal.

Her fasting lipid profile revealed a total serum cholesterol of 260 mg/dl, triglycerides of 52, HDL of 178 with a low-density lipoprotein (LDL) of 72. Serum electrolytes, creatinine, and complete blood counts were within normal limits.

CETP Deficiency

Based on her history, the physical exam and laboratory results the patient may have a deficiency in cholesteryl ester transfer protein (CETP). The presence of an inherited genetic mutation is more likely given a similar lipid abnormality in her identical twin sister. The initial description of this condition was in 1989 with the characterization of a family in Japan with CETP deficiency due to a splicing defect of the CETP gene (1, 2). Family members homozygous for the mutation had moderate hypercholesterolemia, greatly increased HDL and decreased LDL. Family members heterozygous for the mutation had CETP levels in the lower range of normal and moderately increased HDL. No

family members had premature coronary artery disease and there was a tendency toward long life span.

CETP and HDL Physiology

CETP plays an important role in HDL metabolism (3). Apolipoprotein (Apo)-A1 is the predominant lipoprotein found on HDL and originates in the liver. Circulating lipid poor Apo-A1 acquires cholesterol from peripheral tissue through interaction with the ATP-binding cassette A1 protein (ABCA1), which transports free cholesterol from peripheral cells to the nascent HDL particle. Mutations in the ABCA1 gene result in Tangier disease which is characterized by very low HDL levels and cholesterol accumulation in peripheral tissues (4). Free cholesterol in the nascent HDL particle is esterified by lecithin:cholesterol acyl-transferase (LCAT) into cholesterol esters which migrate to the inner core of the maturing particle. Mature HDL particles can interact with scavenger receptors to deliver cholesterol to the liver. The net effect of this pathway for HDL metabolism is removal of cholesterol from peripheral tissues. CETP provides an alternate route for cholesterol movement by stimulating the exchange of cholesterol esters from Apo-A rich HDL particles to Apo-B containing LDL and very low-density lipoprotein (VLDL) particles. HDL acquires triglyceride in exchange for the cholesterol esters. The consequence of CETP action is to transfer cholesterol esters into VLDL and LDL and move triglyceride from these particles into HDL. The role of CETP in transferring triglycerides into HDL may explain why patients with hypertriglyceridemia have low HDL levels.

CETP and Atherosclerosis

CETP has several pro-atherogenic and anti-atherogenic actions. The net effect of the enzyme is to reduce HDL levels and raise serum LDL concentrations. In

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addition, CETP generates triglyceride-rich HDL that is acted on by tissue lipases to yield small dense HDL. Apo-A1 tends to dissociate from small dense HDL and is then be excreted by the kidneys and thus lost to the circulation. By transferring cholesterol esters into VLDL and LDL, CETP also raises the proportion of small-dense LDL and IDL. The loss of Apo-A1 from the circulation and increasing proportion of small dense LDL are both considered atherogenic changes. Alternatively, CETP mediates transfer of cholesterol esters to VLDL and LDL, which are eventually taken up by the liver. CETP may thus facilitate cholesterol efflux from peripheral tissues and thus act in an anti-atherogenic manner.

Experimental Evidence

Studies in animals and humans give conflicting results on the role of CETP in promoting atherosclerosis. In rabbits, administration of a pharmacologic inhibitor of CETP led to an increased HDL and decreased progression of atherosclerotic lesions (5). In one study, over-expression of CETP in mice led to increased buildup of atherosclerotic lesions (6), supporting the hypothesis that CETP has pro-atherogenic activity. In a separate study, mice expressing a human CETP transgene had markedly attenuated development of atherosclerosis compared with controls (7), supporting the case of CETP as a protective factor against atherosclerosis. Human studies generally support the view that increased CETP activity is associated with increased risk of coronary artery disease, whereas decreased CETP levels are protective against atherosclerosis. A 7-yr follow-up of over 2000 men in the Honolulu Heart Program revealed that men with an HDL greater than 60 mg/dl had a lower relative risk of CHD compared with men with an HDL less than 40. Furthermore, men with CETP mutations had the lowest risk of CHD, although the difference was not significant (8). A case-control study using the prospective EPIC-Norfolk study group found that elevated CETP levels were associated with increased risk of future coronary artery disease, but only in those with high triglyceride levels (9).

Torcetrapib

The inverse correlation between HDL levels and risk of coronary artery disease has been long known (10). Furthermore, interventions that increased HDL levels reduced risk of future coronary events. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) trial, patients who received gemfibrozil achieved improvements in HDL levels (11). The increase in HDL was significantly associated with reduced cardiovascular events. These results as well the correlation between reduced CETP activity and high HDL levels supported the development of pharmacologic inhibitors of CETP. A recent large trial examined the use of a CETP inhibitor to raise HDL in patients at high cardiovascular risk. Patients taking the study drug (torcetrapib) achieved a 72% increase in HDL cholesterol and 25% reduction in LDL cholesterol (12). Unfortunately, there was a significant increased risk of cardiovascular events and death from any cause in the patients receiving the study drug. In addition, patients receiving torcetrapib had a mean 5.4-mm Hg elevation in systolic blood pressure. In a separate study, patients receiving torcetrapib had substantially raised HDL but also developed increased blood pressure and showed no change in the rate of progression of carotid intima-media thickness (13). The failure to slow the increase in carotid intima-media thickness has put into doubt the anti-atherogenic potential of torcetrapib. It is not clear why there were increased cardiovascular events and higher mortality in patients taking torcetrapib. The medication raised blood pressure in a subset of patients and this may have contributed to the increased risk. Whether the increased risk was caused by raising of the blood pressure, some other unexpected side effect or alterations in lipid dynamics is still unclear. The answer is important not only to the pharmaceutical industry but also to patients carrying mutations in CETP.

Assessment of Patient

In our opinion, the patient with elevated HDL cholesterol likely has no increased risk of cardiovascular disease and may, in fact, be protected from ath-

erosclerosis. This is based on our current understanding of lipid physiology, experimental data from animal models, and a review of the natural history of patients with CETP deficiency. To further characterize the lipid profile in the patient, we have sent serum samples for determination of Apo-A1 levels as well as NMR-based lipoprotein subfraction analysis. We anticipate seeing elevated Apo-A1 and an increased preponderance of large HDL particles. We have also offered her referral to centers with research experience in CETP deficiency. To better quantify her future risk of cardiovascular disease we have referred her for measurement of carotid intima-media thickness, which gives a good estimate of the atherosclerotic burden (14). We have recommended no medical intervention at this time.

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Childrens Hospital Los Angeles Preceptorial Recap

Under the direction of Dr. Mitchell Geffner, Childrens Hospital Los Angeles (CHLA) recently held its third Endocrine Fellows Foundation (EFF) Preceptorship Program in Pediatric Endocrinology and Diabetes in the last 4 yr. Selected fellows from Brown University Hasbro Children's Hospital (Mimi Kim, M.D.), University of Texas Health Sciences Center San Antonio (Anita Swamy, M.D.), Vanderbilt University (Bradley Van Sickle, M.D., Ph.D.), National Institutes of Health (Rebecca Brown, M.D.), and Uniformed Armed Services (Eric Sherman, M.D.) participated in a 2-wk program held November 5–16, 2007.

Highlights of the program included lectures on “Diabetes in the 21st Cen-

tury” (Francine Kaufman, M.D.), “The KidsNFit Obesity Program” (Megan Lipton, Director of KidNfitness), “The TODAY Study” (Daina Dreimane, M.D.), “Childhood Osteoporosis” (Pisit Pitukcheewanont, M.D.), “Pediatric Obesity: Why We Can't Afford to Wait” (Andriette Ward, M.D.), “Thyroid Cancer in Childhood” (Lynda Fisher, M.D.), and “Hormone Resistance: A Sensitive Subject” (Mitchell Geffner, M.D.). Invited lectures were delivered on the topics of “The First Blush of Puberty—The Story of Kisspeptin as Told through Mice and Men” (Stephanie Seminara, M.D. of Harvard Medical School, Boston, MA) and “C-Type Natriuretic Peptide: A Hormone of Growing Interest” (Robert Olney, M.D. of Mayo Medical School,

Jacksonville, FL). Additional programs included: “Living with Diabetes CHLA Style,” “Stem Cells in Diabetes Research,” “Pediatric Surgery,” “Update in Diabetes Technology,” and “A Day at Esoterix Laboratories.” New sessions included: “Hands-on Physiology Laboratory Experience” and “Research Day at the USC Biomedical Campus.”

Visiting fellows had the unique opportunities to preview the Discovery Channel documentary “Diabetes: A Global Epidemic” with Francine Kaufman, M.D. and to partake in the “CARES Foundation Family Symposium” at Cedars-Sinai Medical Center. Finally, the visiting fellows and the CHLA fellows gave brief synopses of their research data to each other and to divisional faculty members.



Case Report

Hyperinsulinemic Hypoglycemia: A Late Complication of Roux-en-Y Gastric Bypass Surgery

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Introduction

Over the past 20 yr, there has been a rapid rise in overweight and obesity rates in the United States. In result, a concomitant rise in demand for bariatric surgery has also been seen. Cur-

rently, two types of bariatric procedures are commonly performed today: the Roux-en-Y Gastric Bypass (RYGB) and the Laparoscopic Adjustable Gastric Banding (LAGB). The former is the most common procedure in the United States, comprising approx-

imately 80% of all bariatric procedures. Generally, the RYGB is more effective than the LAGB, allowing about 61% of excess weight loss, compared with approximately 48% with LAGB (1). The RYGB is also known to reduce or re-

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solve multiple obesity-related morbidities, such as hypertension, hyperlipidemia, and type 2 diabetes mellitus. Its ability to ameliorate type 2 diabetes is noteworthy in that diabetic patients are often able to discontinue their diabetes medication within days after their surgery, before losing any significant weight. Although likely to be multifactorial, a proposed mechanism behind this remarkable effect is an alteration in incretin physiology induced by the intestinal arrangement in RYGB. GLP-1, an incretin produced by intestinal L-cells, has been shown to promote β -cell proliferation and reduce apoptosis. However, an extreme variant of this effect may be responsible for a newly recognized complication with RYGB. Three years ago, two case series were published describing patients who developed hyperinsulinemic hypoglycemia due to nesidioblastosis, occurring a few years after their RYGB (2, 3). We report a case of a patient who developed nesidioblastosis after RYGB, followed by a complicated clinical course.

Case Report

We present a 49-yr-old female with a prior history of type 2 diabetes mellitus, hyperlipidemia, and depression, who received a RYGB in 2005. The surgery itself was unremarkable and, over a few weeks, she ceased to require any diabetes medications. She complied well with her dietary and exercise requirement and was eventually able to discontinue her lipid medications as well. Two years after her surgery, she had lost 27% of her initial body weight. At this time, however, she started complaining of episodic lightheadedness, tremors, and periods of confusion, prompting a neurological evaluation. Her symptoms were attributed to Depakote toxicity, which was changed to another medication, but her symptoms persisted. On an outpatient visit, she was noted to have frequent hypoglycemic episode on her fingerstick log, but she was unsure whether they corresponded to her symptoms. She underwent a supervised 72-h fast, which precipitated a hypoglycemic episode a few hours after her admission. She was found to have a blood glucose of 49 mg/dl with an insulin and C-peptide lev-

els of 14.2 μ IU/ml (2.6–24.9) and 3.4 ng/ml (1.1–4.4), associated with adrenergic symptoms. These results prompted an abdominal CT to search for an insulinoma, which was unremarkable. She then received a mixed meal test with an exaggerated insulin response at 60 min postmixed-meal, followed by slight hypoglycemia approximately 150 min postmixed-meal. These findings generated a suspicion for RYGB-related nesidioblastosis. Because the patient favored surgical over medical therapy, the patient underwent a selective arterial calcium stimulation test to localize the affected pancreatic area. There was a 2-fold insulin gradient at the distribution of the splenic artery, which localized the nesidioblastosis to the pancreatic body and tail. The patient had a distal pancreatectomy with histologic findings consistent with nesidioblastosis.

The patient did well for 4 months, but hypoglycemic episodes quickly recurred. She complained of both fasting and postprandial hypoglycemia, with glucose levels as low as 30–40 mg/dl. A trial of Diazoxide was started, but up-titration was limited by intolerance to side effects. Octreotide was also tried alone and in combination with Diazoxide, but she could not tolerate the medications. After failing both therapies alone and in combination, she was evaluated for a subtotal pancreatectomy. She agreed to the procedure, leaving a 10% pancreas remnant. As before, her pancreatic histology displayed features of nesidioblastosis.

She remained relatively euglycemic throughout her hospitalization, but as an outpatient, she reported fasting fingersticks in the 200s. Because of this, she was started on low doses of prandial and basal insulin. She also had a glucagon-stimulated C-peptide test, which revealed a subnormal C-peptide response, suggesting severe β -cell impairment. However, she required a quick down-taper of her insulin doses as she was experiencing severe hypoglycemic episodes even with very low doses of insulin. Eventually, insulin was discontinued without any episodes of diabetes ketoacidosis or severe hyper-

glycemia. This suggested that her remnant pancreas produced enough insulin to maintain euglycemia, although most of her pancreas had been removed. This was an unexpected finding given the subnormal C-peptide response to glucagon and the extent of the pancreatectomy. It is conjectured that her remnant pancreas may have also been affected with nesidioblastosis.

Discussion

The link between RYGB and nesidioblastosis was initially introduced through case series by Drs. Service and Patti (2, 3). In his article, Dr. Service noted an unusually high proportion of patients with nesidioblastosis among post-RYGB patients compared with the general population. The patients in the case series each underwent a partial pancreatectomy, revealing enlarged islets, hypertrophic β -cells, and periductal cells staining for insulin. These features are consistent with nesidioblastosis.

One potential mechanism behind this is an underlying hyperinsulinemia predating RYGB, as in genetic mutations involving SUR1/Kir6.2, glucokinase, and glutamate dehydrogenase genes. The underlying hyperinsulinemia may have initially led to obesity, then unmasked with rapid weight loss. Another hypothesis focuses on alterations in incretin secretion induced by the change in intestinal anatomy. Ghrelin, glucose-dependent insulinotropic peptide (GIP), and especially glucagon-like peptide 1 (GLP-1) are the most likely culprits. Ghrelin, which antagonizes insulin secretion and action, has been shown to paradoxically decline and lose its prandial pattern after RYGB (4). It has also been noted that GIP and GLP-1 rise as soon as 1 month after RYGB in type 2 diabetics. The rise in GLP-1 is of particular interest because of its proliferating and anti-apoptotic effects on β -cells (5). GLP-1 hypersecretion is likely to be linked to the hastened transit of nutrients to intestinal L-cells after RYGB. In addition to the rise in GLP-1, studies in diabetic rats suggest that isolating the proximal intestines also enhances glucose disposal. It is suggested that the proximal intestines produce a putative

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anti-incretin factor that prevents uninhibited incretin action. Without this anti-incretin factor, incretins are able to exert their effects uninhibited, leading to nesidioblastosis (6). Experience with GLP-1, however, suggests that other factors are at play in causing hypoglycemia. A GLP-1 analog has been marketed for type 2 diabetes therapy, which causes supraphysiologic levels of GLP-1, but there has yet to be a case of hyperinsulinemic hypoglycemia in this population. Also, RYGB clearly outperforms GLP-1 analogs in resolving type 2 diabetes.

As in our patient, affected individuals present with neuroglycopenic and adrenergic symptoms 1–2 yr after their surgery. Hypoglycemic episodes are noted 1–3 h after meals, which worsen in frequency and severity over time. Symptoms resemble dumping syndrome, a common complication of RYGB, which can delay the correct diagnosis. The two can be differentiated by the presence of neuroglycopenic symptoms, which are not expected in dumping syndrome, and the recalcitrance to dietary therapy. Diagnosis starts with a mixed meal test, which often reveals elevated insulin and C-peptide levels at 30 min, followed by hypoglycemia at approximately 60 min. Radiographic imaging of the pancreas is often of little utility, as nesidioblastosis is a histologic finding and not visible on radiographs. To localize the affected area, an insulin gradient using calcium stimulation is utilized. In the selective arterial calcium stimulation test (SACST), calcium is injected into the

gastroduodenal artery (GDA), superior mesenteric artery (SMA), and splenic artery (SA). At least doubling of the insulin level drawn at the right hepatic vein suggests the presence of hyperfunctioning β -cells at the territory of the artery being studied. In general, the GDA supplies primarily the uncinate process and secondarily the pancreatic head, the SMA supplies primarily the head and secondarily the uncinate process, and the SA supplies the body and tail.

Therapeutic options include dietary changes, medications, and surgery. Small, low-carbohydrate meals, supplemented with protein and fats as desired, prevent a robust insulin response. α -Glucosidase inhibitors, which inhibit the breakdown of carbohydrates to monosaccharides, prevent rapid glucose absorption, also attenuating the insulin response. Diazoxide inhibits insulin secretion by activating ATP-dependent potassium channels on β -cells, thereby preventing the depolarization cascade that leads to insulin release. Octreotide is also a potent inhibitor of insulin secretion. Patients who cannot tolerate or are refractory to medical therapy may proceed to a partial pancreatectomy. The extent of the pancreatectomy depends upon the location of the insulin gradient on the SACST. Because the underlying pathology remains, the islets on the remnant pancreas may be eventually affected, requiring a subtotal pancreatectomy (7). Although highly effective against nesidioblastosis, pancreatoprivic diabetes is a potential consequence.

Hyperinsulinemic hypoglycemia has emerged as a new late complication of RYGB. Although a few hypotheses have been proposed, further research is needed to fully define the pathophysiology, identify predisposed patients, and evaluate treatment outcomes. Given the increasing popularity of bariatric surgery, future investigations will hopefully further elucidate this disease process.

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Sixth Annual EFF/ADA Fellows' Forum

The Endocrine Fellows Foundation, in co-sponsorship with the American Diabetes Association, presented the Sixth Annual EFF/ADA Fellows' Forum. The Forum was held on January 31, 2008, in San Francisco, CA. It preceded the ADA's PostGraduate Course.

The Forum provided Fellows in endocrinology training the opportunity to hear and interact with some of the world's most acclaimed thought leaders in various fields of endocrinology.

The program consisted of didactic lectures and pragmatic workshop experiences. Among those presenting lectures were Drs. Ralph DeFronzo (Insulin Resistance Syndrome) and Steven Kahn (Relationship between Insulin Sensitivity and Insulin Release: Importance in Glucose Metabolism).

The various workshops were mentored by Drs. Jack Leahy, Robert Ratner, Brent Wisse, Robert Henry,

Clifford Rosen, Jorge Mestman, Kelly Hunt, and Andrew Drexler.

The comments from the 80 attending Fellows underscored how very appreciative they were of this opportunity. They included "valuable experience," "excellent interactive approach," "outstanding program," and "terrific faculty."

A special "thank you" is extended to sanofi-aventis for providing an educational grant for this Forum.



Jorge Mestman, M.D. (faculty) and Sherman Holvey, M.D., President, Endocrine Fellows Foundation



Drs. Robert Ratner, Derek LeRoith (EFF Board), Kelly Hunt, and Andrew Drexler



Ralph DeFronzo, M.D. (faculty) and Sherman Holvey, M.D., President, Endocrine Fellows Foundation



Additional attendees at the EFF meeting



Clifford Rosen, M.D. (faculty) visiting with Fellows



EFF Fellows at meeting



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The Endocrine Fellows Foundation realizes that, as dedicated medical practitioners, our mentors and peers are our best resource for growth and education. Endocrine Fellows are encouraged to submit ideas and/or articles for publication and will receive a \$300 honorarium for accepted material.

Articles should range from 800–1000 words or two to four typewritten pages. Exceptions for longer or shorter articles may be made based on content. Submissions should include an original manuscript (including all applicable bibliographic references), a diskette containing the article (Word 6.0 preferred, ASCII format also accepted), plus any accompanying photographs, charts, or graphs (graphic accompaniment to submitted articles is highly encouraged).

Figures should be submitted as TIFF or EPS files. Photoshop files are also acceptable. Please submit artwork at the size it should be printed. See <http://cjs.cadmus.com/da> for additional information. Please provide a good quality hard copy for each figure submitted. Please send figures on CD or disk rather than e-mail.

Please note: EFF reserves the right to edit the material as necessary to accommodate the available space. **Your Mentor must review, approve, and sign off on your articles before you submit them to our office.**

If you have a topic that you think would be of interest to our readers, please forward your submission to Marilyn Fishman, Executive Director, The Endocrine Fellows Foundation, 5959 W. Century Boulevard, Suite 550, Los Angeles, CA 90045. For questions, please call (877) 877-6515.

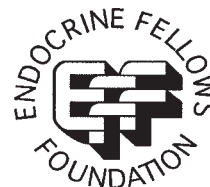
EMPLOYMENT OPPORTUNITIES

Single practicing physician (Endocrinologist) looking for associate doctor—full-time—in Beverly Hills, California, Office. Large practice. Salary is commensurate with time of postgraduate training. Please fax bios to: (310) 652-2269. For information: please call (310) 657-1780.

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San Antonio, Texas. We are seeking a Board Certified or Board Eligible Endocrinologist doctor to work in an eight-physician Endocrine group at the Texas Diabetes Institute (TDI). The TDI is a 153,000 square foot state-of-the-art facility devoted to the care of patients with diabetes and includes all

medical and surgical subspecialties devoted to the comprehensive care of the diabetes patient. The Endocrine physicians must be capable of interacting with a large Diabetes/Endocrine group at the University of Texas Health Science Center including seven other Endocrine physicians. The physician will have a faculty appointment as a Clinical Assistant Professor at the UTHSCSA. The University of Texas Health Science Center at San Antonio (UTHSCSA) is an equal opportunity affirmative action employer. The UTHSCSA offers a competitive salary and generous benefits package. **All faculty appointments are designated as security-sensitive positions.** Interested candidates should contact Ralph A. DeFronzo, M.D., Deputy Director at TDI, Professor of Medicine, and Chief of the Diabetes Division, UTHSCSA (210-567-6691), and e-mail a copy of their CV to Albarado@uthscsa.edu.



To All Program Directors:

Please help us update our database so that

ALL of your Fellows will receive our valuable information, such as:

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Endocrine Specialty: (Circle One) Adult Pediatrics Reproductive Endocrinology

Hospital/University Affiliation: _____

Mailing Address: _____

Outgoing Fellows as of June 2008 are:

Name: _____

Name: _____

New Address: _____

New Address: _____

(If supervising more than two outgoing fellows, please copy the form.)

Program Director: _____ Telephone: _____

E-Mail: _____ Fax: _____

Address: _____

Please Fax Form To: 310-216-0677

Endocrine Fellows Foundation, 5959 W. Century Blvd., Suite #550, Los Angeles, CA 90045

Toll Free: 877-877-6515

EndoTrends QUESTIONNAIRE:



***EndoTrends* is published by the Endocrine Fellows Foundation to provide important, useful, and interesting medical and other relevant information to Endocrine Fellows, young practicing endocrinologists, and the clinical endocrine community in general.**

To help us improve our news magazine and increase its value to you, I would appreciate your thoughts about the following three items:

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Excellent **Somewhat valuable** **Satisfactory**

2. What sections of *EndoTrends* would you like to have emphasized, de-emphasized, or eliminated?

Case Reports	Program Articles	Miscellaneous
More/Less	More/Less	More/Less

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